Relapse of Depression After Electroconvulsive Therapy

To the Editor: Dr Sackeim and colleagues[1] compared relapse rates after electroconvulsive therapy (ECT) among patients who received maintenance antidepressant therapy vs placebo. However, the very low baseline remission rate (55%) reported for ECT is highly atypical.

The authors briefly note that 90% of the patients entering the continuation phase initially received ECT, a method known for its low efficacy, with moderate-dose right unilateral ECT, administered at a dose of 150% above seizure threshold. However, this method is not very effective. In a prospective, randomized, double-blind clinical study reported less than a year ago, Sackeim et al[2] were able to obtain only a 30% remission rate with right unilateral ECT administered at 150% above threshold, a remission rate no better than that typically obtained with placebo in controlled trials of antidepressant drugs. In this prior study,[2] patients who did not show substantial improvement with 150% above the threshold for right unilateral ECT after 5 to 8 treatments were then switched to bilateral ECT. However, neither the number of patients requiring such a switch nor the efficacy of that switch was presented.

It is unfortunate that Sackeim et al based their follow-up study on a sample of patients receiving an inadequate form of ECT. Not only does this present an unwarranted negative impression of the efficacy of ECT in major depression, but it also biases the continuation pharmacotherapy phase in favor of the exceptionally high relapse rates reported because as the authors point out: "Patients with higher [depression scale] scores at the start of the continuation trial had shorter survival time."

Richard Abrams, MD
Department of Psychiatry
Chicago Medical School
Chicago, Ill

Financial Disclosure: Dr Abrams is an officer of Somatics LLC, a manufacturer of electroconvulsive therapy equipment.

1. Sackeim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *JAMA*. 2001;285:1299-1307.
2. Sackeim HA, Prudic J, Devandand DP, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry*. 2000;57:425-434.

To the Editor: The study by Dr Sackeim and colleagues[1] on prevention of relapse of major depression after ECT highlights 2 important goals in the treatment of major depression: the need to continue to treat patients in the acute phase until they achieve remission and the need to continue antidepressant treatment to reduce the risk of relapse. We reviewed the literature as well as package inserts of the serotonin selective reuptake inhibitor (SSRI) antidepressants to compare clinical designs and outcomes used in relapse prevention trials. Key observations are as follows: (1) None of the newer antidepressants now on the market were required to demonstrate efficacy in preventing relapse as a prerequisite for marketing approval in the United States.

(2) All the SSRI antidepressants have now been studied in relapse prevention trials that have shown statistically significant reductions in relapse rates compared with placebo. However, none of the package inserts of these agents uses a standardized format to allow readers to determine the criteria used to define relapse or the actual relapse rates for drug vs placebo.

(3) A review of the literature on relapse prevention reveals a lack of uniformity in almost all aspects of trial design. The duration of acute therapy, design of the acute phase (blinded vs open), criteria used to define remission, duration of the relapse prevention trial, and most importantly, the criteria used to define relapse varies from trial to trial (TABLE).[2-5] Even studies that have defined remission or relapse using the same symptom rating scale (eg, the Hamilton Rating Scale for Depression [HRSD]) have used different versions (eg, 17-item, 21-item, or 24-item scale) of this scale.

(4) To date, there are no published direct comparisons of any of the SSRI antidepressants in adequately powered placebo-controlled long-term studies.

(5) To our knowledge, there also are no published studies that have systematically compared various strategies (eg, dose escalation vs augmentation vs switching) for the treatment of patients who experience relapse while taking a SSRI antidepressant.

These gaps in knowledge are not the fault of the pharmaceutical industry, whose responsibilities are to meet regulatory standards, but are issues that the entire field urgently needs to address. More than half of all patients with depression will experience a relapse and/or recurrence during their lifetimes.[6] Treatment selection for a depressive relapse will remain an art

GUIDELINES FOR LETTERS. Letters discussing a recent *JAMA* article should be received within 4 weeks of the article's publication and should not exceed 400 words of text and 5 references. Letters reporting original research should not exceed 500 words and 6 references. All letters should include a word count. Letters must not duplicate other material published or submitted for publication. Letters will be published at the discretion of the editors as space permits and are subject to editing and abridgment. A signed statement for authorship criteria and responsibility, financial disclosure, copyright transfer, and acknowledgment is required for publication. Letters not meeting these specifications are generally not considered. Letters will not be returned unless specifically requested. Also see Instructions for Authors (January 3, 2001). Letters may be submitted by surface mail: Letters Editor, *JAMA*, 515 N State St, Chicago, IL 60610; e-mail: JAMA-letters@ama-assn.org; or fax (please also send a hard copy via surface mail): (312) 464-5824.

Letters Section Editors: Stephen J. Lurie, MD, PhD, Senior Editor; Jody W. Zylke, MD, Contributing Editor.

Table. Selected Placebo-Controlled Relapse Prevention Trials of SSRI Antidepressants*

Trial	Entry Criteria	Definition of Relapse
Fluoxetine hydrochloride[2]	17-Item HDRS score ≤7	HDRS score >14 for 3 weeks or met the *DSM-IV* criteria
Sertraline hydrochloride[3]	CGI-I ≤2	CGI-S ≥4
Paroxetine hydrochloride[4]	21-Item HDRS score ≤8	At least 1 of the following: CGI-S ≥4 or increase in CGI score of at least 2 points or met the *DSM-III-R* criteria or opinion of investigator or depressive symptoms >7 days
Citalopram hydrobromide[5]	MADRS ≤12	MADRS ≥25 and clinical judgment

*HDRS indicates Hamilton Depression Rating Scale; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity of illness; *DSM-III-R*, *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*; and MADRS, Montgomery-Asberg Depression Rating Scale.

and not a science until more studies like that of Sackeim et al are conducted.

P. Murali Doraiswamy, MD
Ann C. Scates, PharmD
Departments of Psychiatry, Medicine, and Pharmacy
Duke University Medical Center
Durham, NC

Financial Disclosure: Dr Doraiswamy has received grants and/or honoraria from Lilly, Forest, SmithKline Beecham, Glaxo, Pfizer, Wyeth, Organon, Pharmacia, and Bristol-Myers Squibb, but he does not own stock in these companies. Dr Scates has received honoraria from Forest and Pharmacia.

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In Reply: Dr Abrams contends that in our continuation pharmacotherapy study the remission rate of 55% for open-phase treatment with ECT was low and this was due to 90% of patients receiving right unilateral ECT with an inadequate electrical dose.[1] Abrams incorrectly describes our treatment methods. While the minimal dose was 150% above seizure threshold, a higher dose often was used. In addition, of the 262 patients who started with right unilateral ECT, 50.3% were switched to bilateral ECT and received a mean (SD) of 7.1 (4.3) bilateral ECT treatments. Overall, the remission rate for patients treated only with right unilateral ECT was 68.5% compared with 43.8% for patients who were switched to bilateral ECT or who were treated with only bilateral ECT ($\chi^2_1=17.68$, $P<.001$).

Three factors should be considered in evaluating the ECT remission rate. First, our remission criteria were strict, requiring a 60% reduction in HRSD scores and a maximum score of 10 both immediately following ECT and 4 to 8 days later. Of the 176 initial patients who were remitters immediately following ECT, 9.7% had not remitted at the second assessment. In pharmacological trials of major depression, the most common definition of response is simply a 50% reduction in HRSD scores. In our study, 84.2% of patients met this weaker criterion immediately following ECT. Second, we have shown in our study[1] and other samples[2,3] that patients with established medication resistance during the index episode have an inferior response to ECT. Among patients with nonpsychotic depression, the remission rate was 69.5% among those who had not received an adequate medication trial during the episode compared with 47.1% among those exhibiting medication resistance ($\chi^2_1=8.61$, $P=.003$). Overall, 72.2% of 212 patients with nonpsychotic depression met the criteria for medication resistance. Third, only a minimum of 5 ECT treatments was required for patients to be included in the ECT efficacy analyses. This was done to avoid bias due to early withdrawal. However, 8 ECT treatments may be considered minimal for defining an adequate ECT trial.[4] Of those patients who were nonremitters, 38.5% received fewer than 8 treatments.

Abrams suggests that the continuation pharmacotherapy trial was biased in favor of high relapse rates because of the insufficent symptomatic improvement during the ECT phase. Because of the strict remission criteria, the 84 patients in the continuation trial had minimal symptoms, with a mean (SD) HRSD score of 5.5 (3.0) at trial outset and an improvement of 83.9% (9.3%) relative to pre-ECT baseline. This low level of symptoms is classified as remission by virtually all experts in the field.[5,6]

Drs Doraiswamy and Scates point out that patients with major depression are at risk of frequent relapse or recurrence, but US regulatory requirements for approval of antidepressant medications do not require demonstration of efficacy in relapse prevention. They also note that there has been little standardization in the methods used to demonstrate effective relapse prevention. These are serious concerns, because most patients with major depression require long-term treatment. Standardization in methods used to assess both acute efficacy and effectiveness in relapse prevention is needed. We hope that our study contributes to this goal.

Harold A. Sackeim, PhD
Department of Biological Psychiatry
New York State Psychiatric Institute
Departments of Psychiatry and Radiology
Columbia University
New York

1. Sackeim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *JAMA*. 2001;285:1299-1307.
2. Sackeim HA, Prudic J, Devanand DP, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry*. 2000;57:425-434.

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Relationship Between Postmenopausal Hormone Replacement Therapy and Ovarian Cancer

To the Editor: Dr Rodriguez and colleagues[1] found a direct association between the use of hormone replacement therapy (HRT) and the risk of ovarian cancer. Data from other cohort and case-control studies, however, are less consistent.[2]

To further explore this issue, we updated the analysis of a collaborative reanalysis of European case-control studies of ovarian cancer.[3] The present analysis study included 2501 women with histologically confirmed epithelial ovarian cancer and 5882 controls enrolled in 5 case-control studies: 2 were conducted in Greece, 1 in the United Kingdom, and 1 in Italy between 1979 and 1991, all previously reported,[3] plus another case-control study conducted in 4 Italian locations between 1992 and 1999.[4]

The 5 original datasets were combined in a uniform format that included comparable variables, such as age, socioeconomic level, parity, oral contraceptive use, menopausal status, type of menopause, age at menopause, as well as HRT use, duration of use, and time since last use. Odds ratios (ORs) were estimated using unconditional logistic regression models, including the above terms plus study center.

The TABLE shows the distribution of ovarian cancer cases and controls according to HRT use and the corresponding multivariable ORs. In comparison with women who had never used HRT, the OR for ever users was 1.28 (95% confidence interval [CI], 1.05-1.56). The risk was 1.11 for use less than 2 years and 1.41 for use 2 years or more. With reference to time since last HRT use, the OR was 1.37 for less than 10 years since last use, 1.13 for 10 to 14 years, and 0.95 for 15 or more years since last use. By comparison, Rodriguez et al[1] found relative risks (RRs) of 1.51 (95% CI, 1.16-1.96) for ever users and 2.20 (95% CI, 1.53-3.17) for those who used HRT for 10 or more years.

Table. Use of HRT Among Patients With Ovarian Cancer and Matched Controls*

	No. of Cases	No. of Controls	OR (95% CI)†
HRT use			
Never	2330	5385	1.00 (Referent)
Ever	171	297	1.28 (1.05-1.56)
Duration of HRT use, y‡			
Never	2030	4806	1.00 (Referent)
<2	75	156	1.11 (0.83-1.48)
≥2	46	75	1.41 (0.97-2.05)
Time since last HRT use, y‡			
Never	2030	4806	1.00 (Referent)
<10	65	108	1.37 (1.00-1.89)
10-14	20	42	1.13 (0.66-1.95)
≥15	29	72	0.95 (0.61-1.48)

*HRT indicates hormone replacement therapy; OR, odds ratio; and CI, confidence interval.
†Estimates from unconditional logistic regression models, including terms for age, study center, sociocultural level, parity, oral contraceptive use, menopausal status, type of menopause (natural or surgical), and age at menopause.
‡The sum does not add up to the total because of some missing values. Information on duration of use and time since last use was not provided by 1 Greek study[5] and 1 United Kingdom study.[6]

Our updated analysis, including the largest number of ovarian cancer cases from a European population, gives further support to the hypothesis of a moderately positive association of HRT use in menopause with ovarian cancer risk, with a pattern of risk similar to that well known for breast cancer.[7]

Cristina Bosetti, ScD
Eva Negri, ScD
Istituto di Ricerche Farmacologiche "Mario Negri"
Milan, Italy
Silvia Franceschi, MD
International Agency for Research on Cancer
Lyon, France
Dimitrios Trichopoulos, MD
Department of Epidemiology and Center for Cancer Prevention
Harvard School of Public Health
Boston, Mass
Valerie Beral, MD
Imperial Cancer Research Fund
Cancer Epidemiology Unit
Radcliffe Infirmary
University of Oxford England
Carlo La Vecchia, MD
Istituto di Statistica Medica e Biometria
Università degli Studi di Milano
Milan, Italy

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To the Editor: Dr Rodriguez and colleagues[1] suggest that if others confirm their findings, a possible increase in risk of dying from ovarian cancer should be added to the list of possible estrogen-related adverse effects to be discussed with patients considering HRT. They based this recommendation on finding that 31 women died from ovarian cancer among women who in 1982 self-reported using HRT for 10 years or more. This is a relatively small number of events, which weak-

ens the reliability of the conclusions. In addition, other reports on the effect of HRT use on ovarian cancer risk are inconsistent. Of the 5 case-control studies cited by Rodriguez et al that measured ovarian cancer risk among women who used HRT for 5 or more years, 4 found no statistically significant difference.[2-4] One study found a statistically significant increased risk of endometrioid ovarian adenocarcinoma among women who used unopposed estrogen (OR, 2.81; 95% CI, 1.15-6.89).[5] For the more common serous carcinomas, the OR of 2.03 was barely statistically significant (95% CI, 1.04-3.97). A recent meta-analysis reported no association between HRT use and ovarian cancer.[6]

Approximately 11 million US women routinely use postmenopausal HRT. The positive effects of HRT on bone metabolism and the lower genital tract mucosa of women are well documented. In women who still have a uterus, the increased risk of endometrial cancer associated with unopposed estrogen use can be negated by the concomitant use of progestins. The impact, if any, of HRT on the risk of developing breast or ovarian cancer remains controversial.

The study by Rodriguez et al should motivate further investigation of whether an association exists between ovarian cancer and postmenopausal HRT use. However, the existing data are not strong enough to cause an immediate change in clinical practice.

Enrique Hernandez, MD
Division of Gynecologic Oncology
Temple University School of Medicine
Philadelphia, Pa

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In Reply: The findings of Dr Bosetti and colleagues support the association that we observed between ovarian cancer and HRT use. In both analyses, the increased risk diminished after cessation of use. The critical question for clinical practice continues to be whether estrogen and progestin in combination or only unopposed estrogen use affects ovarian cancer risk.

We agree with Dr Hernandez that the data relating ovarian cancer to ever users of HRT are inconsistent. Case-control studies assessing ovarian cancer risk with 5 or more years of HRT use, however, have consistently reported increased risk, as we mentioned in our article. Nevertheless, we agree with Hernandez that the current evidence is incomplete and does not warrant an immediate change in clinical practice. Hernandez does, however, raise a more general and relevant question. When is the evidence from observational data sufficient to change medical practice? In the case of postmenopausal HRT, appropriate guidelines for individual women ultimately should be based on a full understanding of the balance between risk and benefits. Hernandez states that the association between postmenopausal HRT and breast and ovarian cancer is controversial. While we agree with this statement as it relates to ovarian cancer, we believe that the positive association between breast cancer and HRT use has been clearly established.[1,2] Results from the Women's Health Initiative Trial will help clarify the impact of HRT use on risk of cardiovascular disease, osteoporosis, and breast cancer. The effect of postmenopausal HRT use on relatively rare diseases, such as ovarian cancer, cannot be studied with randomized trials and will likely only be evaluated through epidemiologic studies.

Carmen Rodriguez, MD, MPH
Eugenia E. Calle, PhD
Eric J. Jacobs, PhD
Alpa V. Patel, MPH
Michael J. Thun, MD, MS
Department of Epidemiology and Surveillance Research
American Cancer Society
Atlanta, Ga

1. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA*. 2000;283:485-491.
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Breast Cancer in Women With HIV/AIDS

To the Editor: Drs Frisch and colleagues[1] reported that breast cancer was the only malignancy, at least in women, to exhibit a statistically significant pattern of decreasing relative risk (RR) with increasing amounts of time following a diagnosis of acquired immunodeficiency syndrome (AIDS). A recent study also found a statistically significant decrease in the incidence of breast cancer, in both men and women, following the AIDS epidemic in Tanzania.[2] Furthermore, some studies[3] have found that immunosuppressed transplant recipients have a diminished incidence of breast cancer relative to other malignancies. This is contrary to what one would expect, since human immunodeficiency virus (HIV) infection theoretically increases the susceptibility to malignancy because of an acquired deficiency in immunosurveillance of tumor cells and/or an increased susceptibility to oncogenic viruses.

In an attempt to accumulate cases to determine the clinicopathological correlation of breast cancer in HIV-positive persons at our hospital, we searched the *International Classification of Diseases, Ninth Revision* (*ICD-9*)[4] billing codes of

approximately 1.8 million patients for HIV disease. Of these patients, 2460 had at least 1 diagnostic code for HIV. We then searched these patient records for breast cancer codes and were surprised to find that only 2 patients had both HIV and breast cancer, particularly since our medical center serves as a referral center for patients with breast disease and HIV-related illness.

It is unclear why so few HIV-positive patients are diagnosed with breast cancer. Is this phenomenon related to the fact that patients infected with HIV die before they manifest breast cancer, or are such infected individuals truly protected from developing breast cancer because of some direct or indirect effect on their breast epithelium and/or immune system?

Replication of HIV within human mammary epithelial cells has been shown in vitro to reduce the growth of epithelial cells and to down-regulate their growth-factor receptors.[5] Exactly what role the host's immune response plays in facilitating breast cancer development, however, remains controversial.[6] Unquestionably, the answers will not only advance understanding of the biology of breast cancer but also may provide us further insight into alternative treatment modalities, such as immunotherapy.

Liron Pantanowitz, MD
Department of Pathology
Bruce J. Dezube, MD
Division of Hematology/Oncology
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Mass

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In Reply: As we noted in our article, the negative trend was not accompanied by an overall deficit of breast cancer cases. The 143 breast cancers in our study occurring from 60 months before to 27 months after AIDS onset in the cohort of 302834 men and women with HIV infection and AIDS corresponded closely to the expected number (n=135.3) based on incidence rates for the general population (RR, 1.1; 95% confidence interval [CI], 0.9-1.2).

It is difficult to judge whether 2 cases of breast cancer in a group of 2460 HIV-positive individuals treated at the Beth Israel Deaconess Medical Center is more or less than one should expect. This expected number depends strongly on the sex, age, and race composition of this group and on the observation time these individuals were at risk of breast cancer. However, assuming that their patients were similar to our cohort in terms of sex (16.2% female), age, race, and duration of observation, the expected number of breast cancer cases would only be 1.1 ([2460×135.3]÷302834). Even if one third of the cohort that was followed up by Drs Pantanowitz and Dezube was female, the expected number of breast cancer cases (again assuming an age and race composition and a mean follow-up similar to that of ours) would be 2.3, and the corresponding RR would not be significantly reduced (RR, 0.9; 95% CI, 0.1-3.1).

Thus, finding 2 cases of breast cancer in this group does not provide evidence in favor of reduced breast cancer risk in HIV-infected individuals. Whether breast cancer risk is truly influenced by immune dysregulation will remain a difficult issue to settle in the HIV/AIDS setting. Reproductive factors, such as age at first pregnancy, are major epidemiological determinants of breast cancer risk. These factors are likely to differ considerably between HIV-positive and HIV-negative women.

Morten Frisch, MD, PhD
Danish Epidemiology Science Center
Statens Serum Institut
Copenhagen, Denmark
Robert J. Biggar, MD
Eric A. Engels, MD, MPH
James J. Goedert, MD
Viral Epidemiology Branch
Division of Epidemiology and Genetics
National Cancer Institute
Bethesda, Md

A Novel About Bioterrorism

To the Editor: The Association of Pakistani Physicians of North America (APPNA) strongly protests the publication of Dr Panwalker's review of *Germs of War* by Ketan Desai.[1] Panwalker quotes portions of the book that denigrate Pakistan and its people. The passages chosen present slavery as a norm in Pakistan and talk of a group of slaves among whom the protagonist, a future Pakistani physician, learns to inflict "unspeakable acts of cruelty." Subsequently, this capability catches the eye of "the sinister head of Pakistan's intelligence service" culminating in the protagonist's admission to a medical school in Lahore. Finally, Pakistan (a very poor country) is found to be funding US medical research at the Mayo Clinic! Slavery is obviously not practiced in Pakistan; admissions to medical college are not based on recommendations of the Pakistan's secret service, and research on biological weapons is not being carried on in any US university at the behest of Pakistani intelligence agencies.

The executive council of the APPNA believes that publication of material that targets particular nationalities does not constitute an exercise of the right to free speech. We also hope that in the future *JAMA* will demonstrate a better understanding of

the motives underlying such books of "fiction" as well as those of their reviewers.

Raana Akbar, MD
Association of Pakstani Physicians of North America
Westmont, Ill

1. Panwalker AP. Suspense. *JAMA*. 2001;285:1221-1222. Review of: Desai K. *Germs of War*.

In Reply: The task of a book reviewer is to present to potential readers the content of that book and to express a personal opinion about how readable, entertaining, or educational the material is. It is essential for the reviewer to be fair and accurate because much labor has been expended in producing the book. I believe that my review of *Germs of War* is an accurate depiction of the contents of that book. My opinion that it is a compelling story and an entertaining thriller would not be changed if the references to Pakistan had been omitted by the author.

Dr Akbar's statement that "slavery is obviously not practiced in Pakistan" is inaccurate. Sadly, slavery in various forms, including the sale of children, exists in India, Pakistan, and other nations. Although the supreme court of Pakistan abolished forced labor or traffic in 1988 and parliament passed the Bonded Labor (Abolition) Act in 1992 and made the "peshgi" (earnest money) system illegal, these practices continue. A report from the Human Rights Watch/Asia in July 1995 quotes the Human Rights Commission of Pakistan as stating that millions of people are held in debt bondage and the trafficking of women and child servitude continued unchecked.[1]

While Desai clearly states that the characters in the book are fictional, I can imagine how its contents might have an unsettling effect on some individuals or groups. Akbar's assertion that he supports free speech, however, is contradicted by his suggestion that *JAMA* should somehow decipher the motives of book reviewers before publishing their reviews. The resulting specter of censorship might turn away many reviewers who would make honest efforts to evaluate books that they are asked to review.

Anand P. Panwalker, MD
Veterans Affairs Medical Center
Wilmington, Del
Jefferson Medical College
Philadelphia, Pa

1. Contemporary forms of slavery in Pakistan: Human rights watch/Asia. Available at: http://www.hrw.org/reports/1995/Pakistan.htm. Accessibility verified June 15, 2001.

In Reply: *Germs of War* is not intended to and does not denigrate Pakistani physicians in any way. Every ethnic and religious group has individuals in it that can be manipulated by forces of evil, and this book pinpoints one such fictional scenario. Given recent events in Afghanistan and Pakistan, however, I believe that my book presents a possible scenario for biological armageddon.

Ketan Desai, MD, PhD
Spring City, Pa